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EXAMINER
LOEB, BRONWEN

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/780,675	Applicant(s) NICOLAIDES ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2001 and 1 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71* is/are pending in the application.

4a) Of the above claim(s) *32-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,9&11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

This action is in response to the amendment filed 18 July 2001 and the amendment filed 1 March 2002, in which claim 26 was amended and new claim 27 was submitted. New claim 27 was renumbered claim 71 in accordance with 37 CFR 1.126.

Claims 1-71 are pending.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-31 and 71, drawn to a method for making hypermutable bacteria and a composition of such bacteria, classified in class 435, subclass 471 and 252.2 respectively.

   II. Claims 32-50, drawn to a method for generating a mutation in a gene of interest, classified in class 435, subclass 440.

   III. Claims 51-57, drawn to a method for enhancing the mutation rate of a bacterium, classified in class 435, subclass 440.

   IV. Claims 58-70, drawn to a method for generating an MMR-proficient bacterium, classified in class 435, subclass 440.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I-IV are distinct methods from each other, having different starting material, different outcomes and different uses. The invention of Group I comprises introducing into the bacterium a dominant negative allele of a mismatch repair gene, a step not recited in the other methods. The invention of Group II comprises growing a

bacterium comprising both a gene of interest and a dominant negative allele of a mismatch repair gene and testing for mutation in the gene of interest, which is not recited in the other methods. The invention of Group III has a step of exposing a bacterium comprising a dominant negative allele of a mismatch repair gene to a mutagen in order to increase the mutation rate, a step not recited in the other methods. The invention of Group IV has a step of restoring mismatch repair activity to a bacterium after generating a mutation in a gene of interest, a step not recited in the other methods.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and different searches, restriction for examination purposes as indicated is proper. As discussed above, each of the Inventions have steps which are unique to them and which require different, non-overlapping searches.

4. During a telephone conversation with Sarah Kagan on 14 May 2002 a provisional election was made with traverse to prosecute the invention of Group I, claim1-31 and 71. Affirmation of this election must be made by applicant in replying to this Office action. Claims 32-70 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

The Information Disclosure Statement filed 16 August 2001 (Paper #8) was accompanied by four (4) references that were not listed on the Form 1449. These references are: Bell et al (1994) Genomics 19:137-144; Bjornson et al (2000) Biochemistry 39:3176-3183; Kong et al (1999) Molecular Immunology 36:83-91; and Schrader et al (1999) J. Exp. Med. 190:323-330. These references have been considered and therefore have been cited on the attached Form 892 to make them of record.

Sequence Compliance

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers. These sequences include **those on p. 19, line 14 and lines 16-18; p. 20, lines 7-8 and 10-12 and pp. 37-47**. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Specification

7. The disclosure is objected to because of the following informalities: On p. 18, line 11 and p. 25, line 18, there are parenthetical comments apparently unrelated to the specification. On p. 25, the column formatting of Table I needs to be corrected with respect to the column labeled "AMP^R colonies".

Appropriate correction is required.

Claim Objections

8. Claim 71 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 71 is dependent on claim 26 which recites "a protein which consists of the first 133 amino acids of PMS2". Since "consists of" is closed language, claim 26 cannot read on a fusion protein. Thus, the recitation in claim 71 ("a truncation mutation at codon 134") does not further limit the parent claim.

9. Claims 18, 30 and 31 are objected to because of the following informalities: Claim 18 has a grammatically-incorrect comma after the word "hypermutable" in line 1. Claim 30 recites "eukaryotic" and claim 31 recites "eucaryotic". While both are acceptable, one or the other should be chosen for consistency. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-16, 18-25 and 28-31 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 1 is drawn to a method for making a hypermutable bacteria comprising introducing a dominant negative allele of a mismatch repair gene into a bacteria. Claim 18 is drawn to a homogeneous composition of cultured, hypermutable bacteria comprising a dominant negative allele of a mismatch repair gene. These are genus claims in terms of any dominant negative allele of any mismatch repair gene. The specification mentions possible mismatch repair genes for which one can try and find a dominant-negative allele, mentions that over-expression in bacteria of some eukaryotic wild type mismatch repair genes yields a dominant negative effect (which is not the same as a dominant negative allele of a gene) and discloses only one specific known dominant-negative allele of a mismatch repair gene, human PMS2 truncated at codon

134. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the possible dominant-negative alleles of mismatch repair genes based on the teachings in the specification. Other than the truncated human PMS2, there is no disclosure of a correlation between any particular structural features of mismatch repair genes and dominant-negative alleles. There is no disclosure of particular domains of mismatch repair genes in which mutation could render the gene a dominant-negative allele. While the prior art teaches dominant negative alleles of bacterial MutL and MutS (see Aronshtam et al and Wu et al described below), it does not teach any such alleles of eukaryotic homologs of these or the other claimed mismatch repair genes. Furthermore, the over-expression of eukaryotic mismatch repair genes in bacteria which yields a dominant negative phenotype is apparently due to out-competing the endogenous mismatch repair system components for recognition of and binding to mismatches in DNA; in other words, while they might be homologs in terms of sequence, this does not correlate to function, particularly with respect to interaction with other components of the mismatch repair system and the actual repair function. Therefore, the specification does not describe the claimed methods or homogeneous composition comprising a dominant-negative allele of a mismatch repair gene in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these alleles at the time of filing the present application. Thus, the written description requirement has not been satisfied.

12. Claims 1-16, 18-25 and 28-31 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a human PMS2 truncate after codon 133 and for dominant negative alleles of E. coli MutL and MutS, does not reasonably provide enablement for dominant negative alleles of any eukaryotic mismatch repair genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad. Claim 1 is drawn to a method for making a hypermutable bacteria comprising introducing any dominant negative allele of any mismatch repair gene into a bacteria. Claim 18 is drawn to a homogeneous composition of cultured, hypermutable bacteria comprising any dominant negative allele of any mismatch repair gene.

The nature of the invention is a method for making hypermutable bacteria by introducing any dominant negative allele, under control of an inducible promoter, of any mismatch repair gene into the bacteria

An analysis of the prior art as of the effective filing date of the present application shows that the mismatch repair system in prokaryotes is fairly well-understood and numerous homologs of these bacterial components have been identified in eukaryotes (see review by Harfe et al (Annual Review of Genetics (2000) 34:359-399; IDS reference). In bacteria, there are two key components: MutS and MutL, each of which forms a homodimer. Eukaryotes possess mutiple homologs to each of MutS and MutL which form an array of heterodimers; the function of all of these heterodimers is not known. Mutations in some of these eukaryotic homologs are associated with disorders such as hereditary nonpolyposis colon cancer (see for instance Fishel et al (Cell (1993) 75:1027-1038; IDS reference). However, only one dominant negative allele of a eukaryotic gene is known, a truncation in human PMS2. Overexpression of some of these eukaryotic homologs, in wild type form, yields a dominant negative phenotype in bacteria. This result indicates that the eukaryotic homologs cannot functionally interact with any bacterial homologs for mismatch repair, but rather, appear to bind to DNA mismatches and compete out the endogenous system components for binding and thus repair cannot be achieved.

The relative skill of those in the art of mismatch repair is high.

The area of the invention is unpredictable as it is unclear if any of the eukaryotic homologs can be made to interact with the bacterial mismatch repair genes, which is the necessary basis for generating dominant negative alleles of eukaryotic homologs for use in bacteria.

The present specification provides little or no guidance as to which eukaryotic mismatch repair homolog would interact with the endogenous bacteria mismatch repair components such that one could generate a dominant negative allele of the eukaryotic homolog. Indeed, given that one can overexpress eukaryotic homologs and achieve a dominant negative allele, it is unclear why one would go to the trouble of generating a dominant negative allele of any eukaryotic homolog.

No working examples are disclosed using any dominant negative allele of a eukaryotic mismatch repair gene other than PMS2.

The quantity of experimentation necessary to carry out the claimed invention is high as one the skilled artisan cannot rely on either the prior art nor the teachings in the specification for generating a dominant negative allele of any eukaryotic mismatch repair protein that will function as a dominant negative allele in bacteria. First, one would have to determine if any of the known homologs can functionally interact with bacteria mismatch repair proteins. If not, one will have to alter the eukaryotic allele to generate an interaction. Then, one would have to mutagenize and test candidates for being a dominant negative allele in bacteria. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to answer them.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue

experimentation by one of skill in the art to determine how to make and use the claimed methods of making hypermutable bacteria and compositions of the resultant bacteria.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 4, 13, 18, 19 and 29 are rejected under 35 U.S.C. §102(b) as being anticipated by Aronshtam et al (Nucleic Acids Research (1996) 24:2498-2504; cited in the Information Disclosure Statement filed 26 April 2002, Paper #11)). Aronshtam et al teach bacteria transformed with a plasmid (pMQ393) expressing a dominant-negative allele of E. coli mutL. pMQ393 comprises the T7 promoter from pET15b (Novagen). The T7 promoter in pET15b contains a lac operator and is induced by the addition of, for instance, IPTG. See pET-15b Vector (Novagen) May 1999, [online], [retrieved on 8 July 2002] Retrieved using Internet URL:http:/www.novagen.com/SharedImages/TechnicalLiterature/7_TB045.pdf. (This reference is cited only to demonstrate that the T7 promoter is inducible.) Three of these dominant-negative alleles are truncations (722, 723 and 725). See entire document, especially Tables 1 and 4, Figure 2 and p. 2502-2503. The resulting bacteria have hypermutability; see for instance p. 2501, first column, first complete paragraph.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 3, 18 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (Journal of Bacteriology (1994) 176:5393-5400) in view of Winnacker ("From Genes to Clones, Introduction to Gene Technology", Translation by Horst Ibelgaufts, Weinheim, New York, VCH, 1987, pp. 241-242). Wu et al teach bacteria transformed with a dominant negative allele of E. coli mutS gene that results in hypermutability. See entire document. Wu et al do not teach an inducible promoter controlling expression of the dominant negative allele. At the time of the invention, it would have been obvious to one of ordinary skill in the art to use an inducible promoter to express any one of the dominant negative alleles of mutS taught by Wu. One of

ordinary skill in the art would have been motivated to do so because Wu et al teaches that preparing purified preparations for biochemical assays of the mutants (p. 5398, first column, second full paragraph) and it is well known that inducible promoters are preferred to avoid toxicity in bacterial cells and permits the artisan to not overexpress proteins during bacterial division. See Winnacker, p. 241-242.

18. Claims 1, 6, 7, 14, 15, 17, 18, 20, 24-27 and 71 are rejected under 35 U.S.C. §103(a) as being obvious over Nicolaides et al (USP 6,146,894), in view of Winnacker and Aronshtam et al.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. §102(e). This rejection under 35 U.S.C. §103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. §104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was

made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides et al teach a method of making a mammalian cell hypermutable by transforming it with a dominant negative allele of PMS2, and a composition of so-transformed mammalian cells. Nicolaides et al does not teach using a bacterial cell or using an inducible promoter for expressing the dominant negative allele. At the time the invention was filed, it would have been obvious to one of ordinary skill in the art to make bacteria cells hypermutable by transforming them with a dominant negative allele of PMS2 and to have the expression of the dominant negative allele under control of an inducible promoter. One of ordinary skill in the art would have been motivated to do so for several reasons. First, the use of bacteria to create, screen and study protein mutants is extremely well-known and offers known advantages such as the ease of molecular biology manipulations and large-scale culturing. Second, placing the dominant negative allele under the control of an inducible promoter permits control of expression is particularly advantageous to avoid possible toxicity when foreign proteins are overexpressed, for instance, during bacterial division. See Winnacker, p. 241-242. One would have expected success as expression of dominant negative alleles of mismatch repair genes in bacteria was previously demonstrated. See Aronshtam et al.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1, 6, 7, 14, 15, 17, 18, 20, 24- 27 and 71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,146,894 in view of Winnacker and Aronshtam et al. The claims in USP 6,146,894 are drawn to a method of making a mammalian cell hypermutable by transforming it with a dominant negative allele of PMS2, and a composition of so-transformed mammalian cells. At the time the invention was filed, it would have been obvious to one of ordinary skill in the art to make bacteria cells hypermutable by transforming them with a dominant negative allele of PMS2 and to have the expression of the dominant negative allele under control of an inducible promoter. One of ordinary skill in the art would have been motivated to do so for several reasons. First, the use of bacteria to create, screen and study protein mutants is extremely well-known and offers known advantages such as the ease of molecular biology manipulations and large-scale culturing. Second, placing the dominant negative allele under the control of an inducible promoter permits control of expression is particularly advantageous to avoid possible toxicity when foreign proteins are overexpressed, for instance, during bacterial division. See Winnacker, p. 241-242.

One would have expected success as expression of dominant negative alleles of mismatch repair genes in bacteria was previously demonstrated. See Aronshtam et al.

Conclusion

Claims 1-31 and 71 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

July 15, 2002

REMY YUCEL, PH.D
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